Indian Society for Clinical Research
C/o. Pfizer Limited, Pfizer Center, Patel Estate,
Jogeshwari (West), Mumbai – 400 102.
Tel: 022- 6693 2028 and 26774140
Email: info@iscr.org, Website : www.iscr.org

09 February 2015

To,

Dr. Shailendra Kumar
Director (Drugs)
Dept. of Health and Family Welfare
Room No.301 , "D"Wing
Nirman Bhawan,
New Delhi- 110011

Subject: ISCR suggestions on "Drugs and Cosmetics Rules, 1945"

Respected Sir,

This is with reference to the first meeting of the committee set up to examine and recommend amendments in the Drugs and Cosmetics Rules 1945 (Rules), which was held on 21st January, 2015.

ISCR had sent first the draft of the suggestions on the 'Rules' to your office on 31st Jan 2015 (version 1.0 dated 31 Jan 2015).

We herewith submit second draft (version 2.0) of suggestions and recommendations on the 'Rules'. This document includes all comments received by ISCR so far including the comments submitted previously (version 1.0).

We have also approached other organizations to provide their comments; however, we have not yet received comments from any other industry bodies. We will promptly forward to your office any other comments or suggestions that we may receive from other stakeholders in future.

Once again, ISCR would like to thank you for involving ISCR in this extremely important activity.

Please feel free to contact us if there are any questions or comments.

Thank you,

Yours sincerely,

Dr. Shashwati Pramanik
Co-Chair Regulatory Council
Indian Society for Clinical Research

Encl: ISCR comments on Drugs and Cosmetics Rules, 1945 – version 2.0 dated 09 Feb 2015

Suggestions / Recommendations on the Drugs and Cosmetics Rule, 1945

Version 2.0

09 Feb 2015

PREAMBLE: MoHFW (ministry of health and family welfare) has constituted a committee for examining and recommending amendments in the Drugs & Cosmetics Rules 1945. The first meeting of the Committee was held under the Chairmanship of Joint Secretary (Regulation), Department of Health and Family Welfare on 21st January, 2015. ISCR was asked to provide suggestions and recommendations in the Drugs & Cosmetics Rules pertaining to Clinical Trials of drugs.

ISCR has previously submitted initial comments (version 1.0 dated 31 Jan 2015) to MoHFW.

Additional comments which were received post submission of initial draft have been considered and included in this revised document (**Version 2.0**).

Comments/Suggestions:

1: Proposed format of application for conduct of clinical trials

Currently, the Form 44 is the format for "**Application for grant of permission to import or manufacture a New Drug or to undertake clinical trial".** It is proposed to separately include a new & simple form for application for clinical trials. The Form may be called Form 44 A. This form should be used to apply for clinical trials, whether single drug / Fixed dose combination / Biologicals / Vaccines. Proposed format of Form 44 A is given in **Annexure 1**.

There is also a need to provide clarity on which studies require approval which studies does not require permission. ISCR suggests that new rules provide clarity on the matter.

2: Proposed Format of permission for clinical trials

Drugs & Cosmetics Rule 122DA (3) states that "The licensing Authority after being satisfied with the clinical trials, shall grant permission in Form 45 or Form 45-A or Form 46 or Form 46-A, as the case may be, subject to the conditions stated therein". However, **FORM 45 is "***Permission to import Finished Formulation of a New Drug"; FORM 45-A is "Permission to import raw material (new bulk drug substance)"; Form 46 is Permission / Approval for manufacture of a new drug formulation & Form 46 A is Permission / Approval for manufacture of raw material.*

The current format of clinical trial permissions issued by DCGI office does not conform to any of these formats. Hence, it is proposed to include a new form for permission for conduct of clinical trials. The Form may be called Form 45 AA. Proposed format of Form 45 AA is given in **Annexure 2**.

3: Export of biological samples to central laboratories outside India [Export NOC]

Currently there is no provision/rule/forms of issuing Export NOC for exporting the biological samples originating from clinical trial participants to the central laboratory located in other countries. It is proposed to frame rules in this regard and include a new form for application for export of biological samples and permission for exporting biological samples. These Forms may be given name as Form 44 B & Form 45 B respectively. Proposed format of Form 44 B & Form 45 B is given in **Annexure 3** & **Annexure 4**.

4. License for import/Manufacture of investigational drug to be used in clinical trials

There are no specific rules /forms for this licence. Currently the practice followed by CDSCO for import of drugs for clinical trials is as per the rules for import of drugs for the purpose of examiniation, test or analysis (Rule 33, 34, 35, 86, 87, 96-106 etc.). Similarly, the practice followed for the manufacture of drugs for clinical trials is is as per the rules for manufacture of drugs for the purpose of examiniation, test or analysis (Rule 89, 90, 91, 92, 93).

It is important to differentiate between import/manufacture of drugs for the purpose of examination, test or analysis (drugs to be used at testing laboratories) and the import of drugs for the purpose of clinical trials (drugs to be used by the trial participants). It is therefore proposed to include 'clinical trial' term in all associated rules as we have suggested in the existing rules and forms described below or to frame separate rules for import and/or manufacture of drugs for the purpose of clinical trials.

Similarly, there are no dedicated forms for the application and permission grant for import licence for drugs used in clinical trials. Per current practice, Form 11 and 12 are being used and the validity period of 1 year which is applicable for testing and analysis is also being applied for clinicla trials. Hence we are recommending **Form 11AB and Form 12AB** for use of drugs in clinical trials, wherein it is proposed to increase the validity of Import License for the entire duration of clinical trial. Proposed format of separate Form to be used to apply for import/maufacture of drugs for clinical trial are provided in **Annexure 5 & Annexure 6**. Format of permission granted for import/maufacture of drugs for clinical trial are provided in **Annexure 7 & Annexure 8.**

5. Protocol Amendments

As per current practice , applications for Protocol Amendments during the conduct of clinical trial are being made based on the checklists provided by CDSCO. ISCR suggests that elements of these checklists be converted into a proper regulatory framework that can be

included in the Drugs & Cosmetics Rules . Criteria deciding Major and minor protocol amendments should be further clarified and their regulatory approval process should be accordingly amended and included in the rules. Criteria need to be defined for which protocol amendments will be referred for Subject Expert Committee (SEC) deliberations. Currently, protocol amendment approval is a considerable bottle neck in study continuity, and it is taking invariable time because of ambiguity in process followed by HA for approvals.

There are no prescribed rules for addition of Investigator sites and other site related changes. It is proposed to include rules for such amendments in the clinical trial after initial approval is granted by licensing authority.

6. Investigator Undertaking

As per Rule 122 DAB of Drugs & Cosmetics Act, Schedule Y as amended by GSR 53(E) dated 30 Jan 2013; "the Investigator shall report all serious and unexpected adverse events to the Licensing Authority as defined under clause (b) of Rule 21, the Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial and the Ethics Committee that accorded approval to the study protocol, within twenty four hours of their occurrence as per Appendix XI". However, the Appendix VII (Undertaking by the Investigator) clause (x) states "I agree to inform all unexpected serious adverse events to the Sponsor as well as the Ethics Committee within seven days of their occurence."

It is proposed to amend the Appendix VII of the Schedule Y to bring it in alignment with the existing rules.

7. SAE Compensation

See **Appendix 9** for changes suggested in the regulations related to SAE Compensation.

8. Study Status Reports

Rule 122DAC (1) clause (d) states that "Annual status report of each clinical trial, as to whether it is ongoing, completed or terminated, shall be submitted to the Licensing Authority and in case of termination of any clinical trial the detailed reasons for the same shall be communicated to the said Licensing Authority".

There is a need to create a format for submission of ASR to have a consistency across industry in its submission.

9. Changes suggested in Schedule Y

- Schedule Y needs to be split into specific categories.
    1. Requirements AND GUIDELINES for permission to IMPORT AND / OR MANUFACTURE of New Drugs FOR SALE (NDA)
    2. Requirements AND GUIDELINES for permission to UNDERTAKE CLINICAL TRIALS (IND)
- Specific regulations should be included on
    1. Informed Consent (along the lines of 21 CFR part 50)
    2. Ethics Committee (along the lines of 21 CFR 56)

See **Appendix 10** for other changes suggested in Schedule Y.

10. Other Changes

See **Appendix 11** for other changes suggested in Drugs & Cosmetics Rules related to Clinical Trials.

It is pertinent to note that the permissions for conduct of Clinical Trial; permission to import investigational drug for the study and permission to export the biological samples from the trial participants are all issued together. ISCR is fully supportive of this practice and would request this practice to continue.

Annexure 1: Proposed Format of Form 44 A

FORM 44 A

(*See* rules 122A, 122B, 122D and 122 DA)

Application for grant of permission to undertake clinical trial.

I/We*…… of M/s.....…….. (address) hereby apply for grant of permission for clinical trial of …….(drugs names). The necessary information / data is given below :

1. Type of Clinical Study:

   Local/ Global:

   Phase I/ Phase II/ Phase III/ Phase IV/ PMS:

2. Protocol No.
3. Protocol Title:

4. *Particulars of new drug :*

   (1) Name of the drug.

   (2) Dosage form.

   (3) Composition of the formulation :

   (4) Test specification. (i) active ingredients. (ii) inactive ingredients.

   (5) Pharmacological classification of the drug.

   (6) Indications for which proposed to be used.

   (7) Manufacturer of the raw material (bulk drug substances).

   (8) Patent status of the drug.

2. Data submitted along with the application (as per Schedule Y with indexing and page numbers:)

   1. Chemical and Pharmaceutical information.
   2. Animal Pharmacology.
   3. Animal Toxicology.

4. Human / Clinical Pharmacology (Phase I).
5. Exploratory Clinical Trials (Phase II).
6. Confirmatory Clinical Trials (Phase III) (including published review articles)
7. Bio-availability, dissolution and stability study data.
8. Regulatory status of the drug in India and other countries
9. Regulatory status of the study in India and other countries
10. Application for test license
11. Other required information, as may deemed necessary by the new rules

A total fee of rupees.....(in words)..... has been credited to the Government under the Head of Account.....(Original receipt is enclosed).

Dated :.....

Signature…….....

Designation……..

Note: **Delete whichever is not applicable.*

Annexure 2: Proposed format of Clinical Trial Permissions

FORM 45AA

(See Rules 122DA, 122DAA, 122DAB, 122DAC)

Permission for conduct of a clinical trial

Number of the permission and date of issue————

M/s ———————————————— of ———————————————— (address) is hereby permitted to conduct of clinical trial <study identifier> as per the provisions of Drugs & Cosmetics Rules under rule 122DA of the Drugs and Cosmetics Rules, 1945; as per the protocol <*protocol identifier / version number*> submitted to this Directorate.

Investigators approved to participate in the study are as follows:

1)
2)

Dated

Signature

Name and the designation of Licensing Authority

This clinical trial permission is subject to the following conditions:

(a) Clinical trial shall be conducted in compliance with the approved protocols, requirements of Schedule Y annexed to these rules, Good Clinical Practice Guidelines for conduct of clinical trials in India and other applicable regulations;

(b) Approval of the Ethics Committee shall be obtained before initiation of the study;

(c) Clinical trial shall be registered at Clinical Trials Registry of India before enrolling the first patient for the study;

(d) Annual status report of each clinical trial, as to whether it is ongoing, completed or terminated, shall be submitted to the Licensing Authority and in case of termination of any clinical trial the detailed reasons for the same shall be communicated to the said Licensing Authority;

(e) Any report of serious adverse event occurring during clinical trial to the subject, after due analysis, shall be forwarded within **fourteen** days of its **occurrence** as per Appendix XI and in compliance with the procedures prescribed in Schedule Y;

(f) In case of an injury or death during the clinical trial to the subject of the clinical trial the applicant shall provide complete medical management and compensation in the case of trial related injury or death in accordance with Rule 122 DAB and the procedures prescribed under Schedule Y, and the details of compensation provided in such cases shall be intimated to the Licensing Authority in accordance with Rule 122 DAB and the procedures prescribed under Schedule Y.

(g) The premises of Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors and clinical trial sites shall be open to inspection by th e officers authorized by the Central Dr ugs Standard Control Organization, who may be accompanied by an officer of the State Drug Control Authority concerned, to verify compliance to the requirements of Schedule Y, Good Clinical Practices guidelines for conduct of clinical trials in India and other applicable regulations;

(h) The Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors and clinical trial sites and the investigator shall allow officers authorized by the Central Drug Standard Control Organization, who may be accompanied by an officer of the State Drug Control Authority concerned, to enter with or without prior notice, any premises of sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors and clinical trial sites to inspect, search and seize any record, data, document, books, investigational drugs etc. related to clinical trials and provide adequate replies to any queries raised by the inspecting authority in relation to the conduct of clinical trial;

(i) Clinical trial shall be conducted only at those sites which are institutes/hospitals having adequate emergency facilities and duly registered Institutional Ethics committees.

(j) The details of payment honorarium financial support/fees paid by the Sponsor to the Investigator(s) for conducting the study shall be made available to this directorate before initiation of each of the trial sites.

Annexure 3: Application Format For Obtaining Approval For Export of Biological Samples Of Clinical Trial For Testing

Form 44 B
(See Rule xxxxx)

APPLICATION FORMAT FOR OBTAINING APPROVAL FOR EXPORT OF BIOLOGICAL SAMPLES OF CLINICAL TRIAL FOR TESTING

1.	Name and address of the firm		
2.	Details of the study (Protocol Number / Study Name)		
3.	Copy of the permission to conduct the study granted by regularoty authority, if available		
4.	Tentative date completion of clinical trial		
5.	Import export code number (I.E.C. No.)		
6.	Type of sample	Import tariff code (ITC Code)	
7.	Whole blood		
8.	Serum		
9.	Plasma		
10.	Urine		
11.	Others Specify		
12.	Shipment Details: Countries of export		
13.	Name and address of the laboratory where biological samples will be sent		
14.	If sample is to be sent in more than one Laboratory, Details of sample is to be provided for sending the sample in each laboratories		
15.	If application is already submitted in DGFT, provide details of the same.		

Annexure 4: Permission For Export Of Biological Samples Of Clinical Trial For Testing

Form 45 B
(See Rule xxxxx)

PERMISSION FOR EXPORT OF BIOLOGICAL SAMPLES OF CLINICAL TRIAL FOR TESTING

Export permission No.

M/s _____ of _____ (address) is hereby granted permission to export human biological samples obtained from the patients participating in the trial approved by this office, to following laboratory for the purpose of test and analysis only.

Details of the laboratory:

Details of the samples permitted to be exported:

Dated

Signature

Name and the designation of Licensing Authority

Conditions of the license:

- **This permission is valid for the entire duration of clinical trial**.
- This permission is valid to export samples originating from only the study for which this permission is granted.
- The samples should be sent only to the laboratory mentioned in this permission.
- This permission also extends to exporting the biological samples from patients participating at those trial sites which may be subsequently approved by this directorate after grant of initial clinical trial permission.

Annexure 5: Format of application for Import License to import study drug for clinical trials

FORM 12 AB*

[See Rule XXXX]

Application for license to import drugs for purpose of clinical trials

I .. .. .resident of .. . . by occupation.....hereby apply for a license to import the drugs specified below for the purposes of clinical trial to be used by study participants at investigator sites approved by the licensing authority from ..... and I undertake to comply with the conditions applicable to the license.

A fee of rupees _____has been credited to Government under the Head of Account "0210 - Medical and Public Health, 04-Public Heatlh, 104-Fees and Fines" under the Drugs and Cosmetics Rules, 1945 - Central vide Challan No. ……. Dated …… (attached in original).

Protocol Number:

Names of drugs	Quantities permitted to be imported

Date.....

Signature.....

Name & designation of Applicant

Annexure 6: Format of application to manufacture study drug for clinical trials

FORM 30

(*See* rule 90)

Application for licence to manufacture drugs for purposes of examination, test or analysis or clinical trial

1. …….of.....……by occupation.....

hereby apply for licence to manufacture the drugs specified below for purposes of examination, test ~~or~~ analysis or clinical trial at ……. and I undertake to comply with the conditions applicable to the licence.

Names of Drugs

Date..... *Signature……..*

Annexure 7: Format of permission to Import study drug for clinical trials

FORM 11 AB*

[See Rule XXX]

License to import drugs for the purposes of conduct of clinical trial

Import Permission No. Date:

..... of..... is hereby licensed to import from.....the drugs specified below for the purposes of use by participants of clinical trial at ..... or in such other places as the licensing authority may from time to time authorize.

This license is subject to the conditions prescribed in the Rules under the Drugs and Cosmetics Act, 1940.

This license shall, unless previously suspended or revoked, be in force **for the entire duration of clinical trial** :-

Protocol No.:

Names of drugs Quantities which may be imported

Date..... Signature.....

Name & designation of Licensing Authority

Condition of License

1. The Licensee shall use the substances imported under the license exclusively for purpose of clinical trial at the places specified in the license, or in such other places as the Licensing Authority may from time to time authorize.
2. The Licensee shall allow any inspector authorized by the Licensing Authority in this behalf to enter, with or without prior notice, the premises where the substances are kept, and to inspect the premises, and investigate the manner in which the substances are being used to take samples thereof.

3. The Licensee shall keep a record of, and shall report to the Licensing Authority, the substances imported under the license, together with the quantities imported and the date of importation.
4. The Licensee shall comply with such further requirements, if any, applicable to the holders of licenses as may be specified in any rules subsequently made under Chapter III of the Act and of which the Licensing Authority has given to him not less than one month's notice.
5. The drugs imported under this license shall not be directed to or for Commercial Marketing including export purposes.
6. The Firm shall obtain No Objection Certificate from the Narcotics Commissioner of India, 19, The Mall Morar, Gwalior for the import of drugs under Narcotic Drugs and Psychotropic Substances Act and Rules, 1985.

Annexure 8: Format of permission to manufacture study drug for clinical trials

FORM 29
(*See* rule 89)
License to manufacture drugs for purposes of examination, test or analysis or clinical trial

1. … …….....of……..

is hereby licensed to manufacture the drugs specified below for purposes of examination, test or analysis or clinical trial at ……

2. This license is subject to the conditions prescribed in Part VIII of the Drugs and Cosmetics Rules, 1945.

3. This license shall be in force for one year from date specified below.

Names of drugs

Date : …… ***Licensing Authority……***

Annexure 9: Suggestions in Drugs & Cosmetics Rules related to SAE Compensation

Reference Section	ISCR Recommendations	Rationale
Rule 122DAB clause 5 (c) Failure of investigational product to provide intended therapeutic effect , where, the standard care, though available, was not provided to the subject as per the clinical trial protocol; And, Appendix XII Clause 5 (d) Failure of investigational product to provide intended therapeutic effect where, the standard care, though available, was not provided to the subject as per the clinical trial protocol	The clause should be deleted	The purpose of conducting a clinical trial is to test investigational products for safety and efficacy (i.e. the principle of "clinical equipoise"). There can be no guarantee as to the therapeutic effect of the drug under clinical investigation. The patient is duly informed of the investigational nature of the study through the informed consent process. As the relatedness to the study is assessed for each serious adverse event this would also ensure that the study participant gets free and appropriate medical management and compensation as under clause (b) of Rule 21."

Rule 122DAB clause 5 (e) Adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol; And, Appendix XII clause 5 (f) Adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol	Suggestion: modify the clause as follows: Adverse effects due to concomitant medication, **i) if used for any indication other than that approved in the drug label** **ii) which are unexpected (i.e. not part of the approved label of the drug),** excluding standard care, necessitated as part of approved protocol	Concomitant medication will always be part of a clinical trial as a subject can have other comorbidities other than that under for which the trial is being conducted. (e.g. a patient in a diabetes trial may have hypertension and/or dyslipidemia for which the patient may be on an drug which is standard of care for that condition) . If concomitant medication is used for any indication outside the approved label of the drug then it would be deemed as testing for a new indication which falls into the category of clinical trial for a new drug and needs approval from agency in the first place.
As per the current regulations SAE reporting timeline starts from the SAE Occurrence	ISCR propose to change this reporting timeline from SAE awareness	There are many cases where the site/investigator does not become aware of SAE on the day of the occurrence, especially in trials where subjects are outpatients. As per ICH GCP guidelines (ICH E2A: Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the reporting timelines for SAEs begin with "awareness" of SAE.
Schedule Y: Format of informed consent form for Subjects participating in a clinical trial The format requires to furnish information	Suggest deletion of requirement to capture Qualification and Occupation of the patient.	In the Compensation formulas (see below) Qualification and Occupation is not required for calculation of quantum of compensation in clinical trial injury or SAEs leading

regarding qualification and occupation of the participant		to death. It also puts an administrative burden on investigator/site as they would not be able to attest for the veracity of subjects qualification/occupation based on documents submitted. Ref: FORMULA TO DETERMINE THE QUANTUM OF COMPENSATION IN THE CASES OF CLINICAL TRIAL RELATED SERIOUS ADVERSE EVENTS (SAES) OF DEATHS OCCURRING DURING CLINICAL TRIALS (Released in June 2014) and FORMULAE TO DETERMINE THE QUANTUM OF COMPENSATION IN THE CASES OF CLINICAL TRIAL RELATED SERIOUS ADVERSE EVENTS OF INJURY OTHER THAN DEATHS OCCURRING DURING CLINICAL TRIALS (Released in Dec 2014)

Appendix 10: Comments on Schedule Y

Reference Section	ISCR Recommendations	Rationale
Section 1; Clause (2) "If the study drug is intended to be imported for the purposes of examination, test or analysis, the application for import of small quantities of drugs for such purpose should also be made in Form 12"	It is proposed to include new forms for application and permission for importing study drugs (**Form 12AB and Form 11AB**)	It is important to differentiate between import/manufacture of drugs for the purpose of examination, test or analysis (drugs to be used at testing laboratories) and the import of drugs for the purpose of clinical trials (drugs to be used by the trial participants). It is therefore proposed to include 'clinical trial' term in all associated rules or to frame separate rules for import and/or manufacture of drugs for the purpose of clinical trials.
	It is proposed to make the Import license valid for the entire duration of clinical trial	For logistic and administrative ease.
Section 1; Clause (3) For drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority.	Modify the clause as "For drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario **or drugs for unmet medical needs and orphan drugs**, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the	**Reference** "Report of Prof Ranjit Roy Chaudhury Expert Committee" "Waiver of clinical trials may be considered if the study is designed to evaluate or examine public health emergencies, e.g. 1ll epidemic situations when there is a need for emergency healthcare services to respond to a disaster, significant

	Licensing Authority." For additional indications of already marketed drugs, clinical data requirements may be abbreviated or deferred or omitted based on existing safety data in India patients	outbreak of an infectious disease, bioterrorist attack or any other significant or catastrophic event, and the health consequences have the potential to overwhelm routine community capabilities."
2. Clinical Trial : **(1) Approval for clinical trial** **(i)** Clinical trial on a new drug shall be initiated only after the permission has been granted by the Licensing Authority under rule 21 (b), and the approval obtained from the respective ethics committee(s). The Licensing Authority as defined shall be informed of the approval of the respective institutional ethics committee(s) as prescribed in Appendix VIII, and the trial initiated at each respective site only after obtaining such an approval for that site. The trial site(s) may accept the approval granted to the protocol by the ethics committee of another trial site or the approval granted by an **independent ethics committee** (constituted as per Appendix VIII), provided that the approving ethics committee(s) is/are willing to accept their responsibilities for the study at such trial site(s) and the trial site(s) is/are	Independent Ethics Committee can review only study protocol & related documents of BA/BE studies. Clarify whether the statement highlighted still applies for phase II-III studies	To align with the new regulations

willing to accept such an arrangement and that the protocol version is same at all trial sites.		
2. Clinical Trial : **(1) Approval for clinical trial** **(ii)** …. If services of a laboratory or a facilities outside the country are to be availed, its/their name(s), address(s) and specific services to be used should be stated in the protocol to avail Licensing Authority's permission to send clinical trial related samples to such laboratory(ies) and/or facility(ies). …	Suggest removing this requirement from protocol and include this in other section i.e. permission to export biological samples from clinical trials.	Usually the decision to use central lab facility is taken at much later stage while Protocol gets finalized in very initial phase. It would not be feasible to amend protocol if for any reason central lab mentioned in the protocol is changed (may include minor address change sometimes)
3. Studies in special populations **(1) Geriatrics:** "Geriatric patients should be included in Phase III clinical trials…"	Contrary to the existing rules, CT approval letters provides age clause not to include geriatric population. Suggest not including age restrictions in CT permissions	Provision is already provided within existing rules.
3. Studies in special populations **(4) Post Marketing Surveillance.-**	Clarity regarding PMS studies required. In alignment with ICMR, PMS studies if conducted in approved setting (indication, dose, patient population etc) no approval from licensing authority is needed.	Bring consistency between different regulations
Appendix VII – Undertaking by the Investigator Clause (x): I agree to	Clause should be modified according to the new regulation which has changed timelines for SAE reporting.	Bring consistency between different regulations

inform all unexpected serious adverse events to the Sponsor as well as the Ethics Committee within seven days of their occurrence		

Annexure 11: Other specific suggestions in Drugs & Cosmetics Rules related to Clinical Trials

Rule 31. Standard for certain imported drugs.- No drug shall be imported unless it complies with the standard of strength, quality and purity, if any, and the test prescribed in the rules shall be applicable for determining whether any such imported drug complies with the said standards:
Provided that the drugs intended for veterinary use, the standards of strength, quality and purity, if any, shall be those that are specified in Schedule F(1) and the test prescribed in that Schedule shall be applicable for determining whether any such imported drug complies with the said standards and where no standards are specified in Schedule F(1) for any veterinary drug, the standards for such drug shall be those specified in the current edition, for the time being in force, of the British Pharmacopoeia Veterinary:
Provided further that the licensing authority shall not allow the import of any drug having less than sixty per cent residual shelf-life period as on the date of import:
Provided also that in exceptional cases the licensing authority may, for reasons to be recorded in writing, may allow, the import of any drug having lesser shelf-life period, but before the date of expiry as declared on the container of the drug.

The special conditions/ circumstances under which the permission for import of drug with residual shelf life less than 60% may be considered are as follows:

1. For charity purpose (it should be ensured that the drug is used within the shelf life).
2. The drugs which are required under the National Health Programs/ schemes or for use in emergency situations where there is no substitute available.
3. The drugs required for treatment of diseases which are specific to be of Indian origin.
4. The drugs which are imported only for the testing/ analysis or clinical trial purposes.
5. Orphan drugs for rare diseases.
6. Drugs required for control of sudden outbreak of diseases.
7. Import of unapproved/approved new drug/banned bulk drugs for manufacturing of formulation exclusively for export.

It is required for importers who would import such d rugs shall give proper justification for the import. The application for import of the drug with residual shelf life of less than 60% should be made to the DCG(I) for necessary No Objection Certificate.

Rule 33. Import of drugs for examination, test or analysis or a clinical trial. - Small quantities of drugs the import of which is otherwise prohibited under Section 10 of the Act may be imported for the purpose of examination, test or analysis **or for use in a clinical trial** subject to the following conditions:

(a) No drug shall be imported for such purpose except under a licence in Form 11;
(b) the licensee shall use the substances imported under the licence exclusively for purposes of examination, test or analysis and shall carry on such examination, test or analysis in the

place specified in the licence, or in such other places as the licensing authority may from time to time authorize ;
(c) the licensee shall allow any Inspector authorized by the licensing authority in this behalf to enter, with or without prior notice, the premises where the substances are kept, and to inspect the premises, and investigate the manner in which the substances are being used and to take samples thereof ;
(c) the licensee shall keep a record of, and shall report to the licensing authority, the substances imported under the licence, together with the quantities imported, the date of importation, and the name of the manufacturer;
(d) the licensee shall comply with such further requirements, if any, applicable to the holders of licences for examination, test or analysis **or clinical trial** as may be specified in any rules subsequently made under Chapter III of the Act and of which the licensing authority has given to him not less than one month's notice.

Rule 34. Application for licence for examination, test or analysis or for clinical trial. -
(1) An application for a licence for examination, test or analysis **or for a clinical trial** shall be made in Form 12 and shall be made or countersigned by the head of the institution in which, or by a proprietor or director of the company or firm by which the examination, test or analysis **or clinical trial** will be conducted.
(2) The licensing authority may require such further particulars to be supplied as he may consider necessary.
(3). Every application in Form 12 shall be accompanied by a fee of one hundred rupees for a single drug and an additional fee of fifty rupees for each additional drug.
(4). The fees shall be paid through a challan in the Bank of Baroda, Kasturba Gandhi Marg, New Delhi - 110 001 or any other branch or branches of Bank of Baroda, or any other Bank, as notified, from time to time, by the Central Government, to be credited under the Head of Account "0210- Medical and Public Health, 04-Public Health, 104-Fees and Fine.]

Rule 35. Cancellation of licence for examination, test or analysis or for clinical trial. - (1) A licence for examination, test or analysis **or for clinical trial** may be cancelled by the licensing authority for breach of any of the conditions subject to which the licence was issued.
(2) A licensee whose licence has been cancelled may appeal to the Central Government within three months of the date of the order.

PART VIII
MANUFACTURE FOR EXAMINATION, TEST ~~OR~~ ANALYSIS OR CLINICAL TRIALS

Rule 86. Conditions relating to manufacture for examination, test ~~or~~ analysis or clinical trials - The provisions of Section 18 of the Act shall not apply to the manufacture of any drug in small quantities for the purpose of examination, test or analysis **or clinical trials** if the conditions prescribed in this Part are fulfilled.

Rule 87. Labelling- Any drug manufactured for the purpose of examination, test ~~or~~ analysis **or clinical trials** shall be kept in containers bearing labels indicating the purpose for which it has been manufactured.

Rule 88. Labelling of drugs supplied to other persons- If any drug manufactured for the purpose of examination, test or analysis is supplied by the manufacturer to any other person, the container shall bear a label on which shall be stated the name and address of the manufacturer, the accepted scientific name of the substance if known, or if not known a reference which will enable the substance to be identified and the purpose for which it has been manufactured.

Rule 89. Licence- If the person proposing to manufacture a drug for the purpose of examination, test or analysis **or for use in clinical trials** does not hold a licence in Form 25 or Form 28 in respect of such drugs he shall before commencing such manufacture, obtain a licence in Form 29:
Provided that in the case of a drug the composition of which is such that the drug is not generally recognised among experts qualified by scientific training and experience to evaluate the safety of drugs as safe for use, no licence in Form 29 shall be granted unless the applicant produces a certificate from the "Licensing Authority" mentioned in Rule 21, to the effect that there would be no objection to such licence being granted.

Rule 90. Form of Application- (1) An application for a licence in Form 29 shall be made to the Licensing Authority appointed by the State Government for the purposes of this Part (hereafter in this Part reffered to as the Licensing Authority) in Form 30 and shall be made by or countersigned by the head of the institution in which, or a director of the firm or company by which, the substance will be manufactured.
2) Every application in Form 30 shall be accompanied by a fee of rupees two hundred and fifty.

Rule 91. Duration of Licence- A licence in Form 29 shall, unless sooner cancelled, be in force for a period of one year from the date of issue, and may thereafter be renewed for periods of one year at a time.

Rule 92. Conditions of licence.- A licence in Form 29 shall be subject to the following conditions
(a) the licensee shall use the drugs manufactured under the licence exclusively for purpose of examination, test or analysis **or for clinical trials**, and shall carry on the manufacture and examination, test or analysis **or clinical trials** at the place specified in the licence;
(b) the licensee shall allow an Inspector appointed under the Act to enter, with or without notice, the premises where the drugs are manufactured and to satisfy himself that only examination, test or analysis **or clinical trials** work is being conducted;
(c) the licensee shall keep a record of the quantity of drugs manufacured for examination, test or analysis **or for clinical trials** and of any person or persons to whom the drugs have been supplied;
(d) the licensee shall comply with such further requirements, if any, applicable to the holders of licences in Form 29 as may be specified in any Rules subsequently made under the Act and of which the Licensing Authority has given him not less than one month's notice;

(e) the licensee shall maintain an Inspection Book to enable an Inspector to record his impressions and defects noticed.

Rule 93. Cancellation of licences- (1) The Licensing Authority may, after giving the licensee an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefor, cancel a licence issued under this Part, either wholly or in respect of some of the substances to which it relates, if, in his opinion, the licensee has failed to comply with any of the conditions of the licence or with any provision of the Act or Rules thereunder.
(2) A licensee whose licence has been suspended or cancelled may appeal to the State Government within three months from the date of the order.

Rule 96. Manner of Labelling- (1) Subject to the other provisions of these rules, the following particulars shall be either printed or written in indelible ink and shall appear in a conspicuous manner on the label of the innermost container of any drug and on every other covering in which the container is packed **for commercial use**, namely: -
(i) The name of the drug:
(A) For this purpose the proper name of the drug shall be printed or written in a more conspicuous manner than the trade name, if any which shall be shown immediately after or under the proper name and shall be-
(a) for drugs included in Schedule F or Schedule F(1), the name given therein;
(b) for drugs included in the Indian Pharmacopoeia or the official pharmacopoeias and official compendia of drug standards prescribed in Rule 124, the name or synonym, specified in the respective official pharmacopoeias and official compendia of drug standards followed by the letters 'IP'. or, as the case may be, by the recognised abbreviations of the respective official pharmacopoeia and official compendia of drug standards;
(c) for drugs included in the National Formulary of India, the name or synonym specified therein followed by the letters 'N.F.I.' ;
(d) for other drugs, the international non-proprietary name, if any, published by the World Health Organisation or where an international non proprietary name is not published, the name descriptive of the true nature or origin of the substance.
(e) for investigational drugs to be used in clinical trials, the investigator drug name/code/number should be included

(ii) A correct statement of the net contents in terms of weight, measure, volume, number of units of contents, number of units of activity, as the case may be, and the weight, measure and volume shall be expressed in Metric system.

(iii) The content of active ingredients :- This shall be expressed -
(a) for oral liquid preperations in terms of the content per single dose, the dose being indicated in 5 millilitres :
Provided that where the dose is below 5 millilitres the contents of active ingredients may be expressed in terms of one millilitre 11[or fraction thereof:
Provided further that where the single dose is more than 5 millilitres, the content of active ingredients shall be expressed in terms of minimum single dose as approved by the licensing authority.

(b) for liquid parenteral preparations ready for administration, in terms of 1 millilitre or percentage by volume or per dose in the case of a single dose container : Provided that if the preparation is contained in an ampoule it will be enough if the composition is shown on the label or wrapper affixed to any package in which such ampoule is issued for sale;
(c) for drugs in solid form intended for parenteral administration in terms of units or weight per milligramme or gramme;
(d) for tablets, capsules, pills and the like, in terms of the content in each tablet, capsule, pill or other unit, as the case may be;
(e) for other preparations, in terms of percentage by weight or volume or in terms of unitage per gram or millilitre as the case may be ;
Provided that clause (iii) shall not apply to a pharmacopoeial preparation where the composition of such preparation is specified in the respective pharmacopoeia and to a preparation included in the National Formulary of India ;
(iv) The name of the manufacturer and the address of the premises of the manufacturer where the drug has been manufactured.
it shall be enough if only the name of the manufacturer and his principal place of manufacture is shown.
(v) A distinctive batch number, that is to say, the number by reference to which details of manufacture of the particular batch from which the substance in the container is taken are recorded and are available for inspection, the figure representing the batch number being preceded by the words 'Batch No.' or 'B.No. ' or 'Batch' or 'Lot No.' or 'Lot'.
Notes- (1) In the case of drugs manufactured by continuous process, like manufacture of magnesium sulphate, pharmaceutical chemicals, etc., the production resulting in one homogeneous mix of the finished products shall be considered as one "Batch".
(2) In the case of powders, liquid orals, ointments, etc., one "Batch Number" shall be assigned to all the containers filled from one homogeneous bulk.
(3) In the case of tablets, capsules, lozenges, troches, etc., one "Batch Number" shall be assigned to the products manufactured from one homogeneous mix ready for compression or filling.
(4) In the case of parenteral preparations sterilized by steam under pressure, one "Batch Number"shall be assigned to all containers filled from one homogeneous bulk solution and sterilized in one sterilizer load.
(5) In the case of containers of parenteral preparations filled from one homogeneous bulk solution and sterilized in more than one sterlizer load, the "Batch Number" as is assigned to the homogeneous bulk solution, provided that samples are taken from all the sterilizer loads pass the sterility test, and are kept separate from one another until the report of the sterility test is available.
Explanation- For the purpose of chemical and other tests, representative samples from all containers filled from the homogeneous bulk solution should be taken.
(6) In the case of parenteral and other sterile products filled aseptically, a "Batch Number" shall be assigned to all containers filled from one homogeneous mix during one filling operation, the filling operation being completed in a period of not more than a day and during which no scheduled change in the filling assembly is made.
When containers are filled from one homogeneous mix in a number of filling operations, the "Batch Number" assigned to the containers filled in individual filling operations shall be the same "Batch Number" as is assigned to the homogeneous mix, provided the samples taken

from all the different filling operations pass the sterility tests, and are kept separate from one another until the report of the sterility test is available.
Explanation- For the purpose of chemical and other tests, representative samples from all containers filled from the homogeneous mix should be taken.
(7) In the case of medicinal gases produced by a continuous process of operation a week's production from one tank load shall be considered as Batch;
(vi) Every drug manufactured in India shall bear on its label the number of the licence under which the drug is manufactured, the figure representing the manufacturing licence number being preceded by the words 'Manufacturing Licence Number ' or
'Mfg. Lic.No.' or 'M.L.'
(vii) Drugs specified in Schedule P and their preparations including combinations with other drugs shall bear on their labels the date of manufacture and the date of expiry of potency, and the period between the date of manufacture and the date of expiry shall not exceed that laid down in the said Schedule under the conditions of storages specified therein. Drugs and their preparations not included in Schedule P, shall bear on their labels the date of their manufacture and also the date of their expiry which shall not exceed sixty months from the date of manufacture:
Provided that this period may be extended by the Licensing Authority specified in clause (b) of Rule 21 in respect of any specified drug if satisfactory evidence is produced by the manufacturer to justify such an extension.
(viii) drugs specified in Schedule C(I) and their preparations including combinations in other drugs shall bear on their labels (a) the date of manufacture, and (b) date of expiry of potency fixed by the manufacturer
Provided that drugs in bulk form included in Schedule C(1) which are not ready for use and not included in Schedule P need not bear on the label the date of expiry of potency].
Provided further that no reference shall be made to any other licence number granted by any authority outside India on any label or container or in any covering in which the container is packed or in any other matter or advertisement enclosed therewith.

(ix) Every drug intended for distribution to the medical profession as a free sample shall, while complying with the labelling provisions under clauses (i) to (viii), further bear on the label of the container the words 'Physician's sample-Not to be sold' which shall be overprinted.

(x) Drug intended for use in clinical trials shall bear on label wordings 'For clinical trial use only-Not to be sold'

(x**i**) If any preparation contains not less than 3 per cent by volume of alcohol the quantity of alcohol shall be stated in terms of the average percentage by volume of absolute alcohol in the finished products.
(x**ii**) In addition to the other particulars which are required to be printed or written under these rules, the label of innermost container of the following categories of drugs and every other covering in which the container is packed shall bear a conspicuous red vertical line on the left side running throughout the body of the label which should not be less than 1 mm in width and without disturbing the other conditions printed on the lable under these rules, namely:-

Narcotic analgesics, hypnotics, sedatives, tranquillisers, corti-costeriods, hormones, hypoglycemics, antimicrobials, antiepileptics, antidepressants, anticoagulants, anti-cancer the above list:
Provided that the provisions of this clause shall not apply to - (a) preparations intended for animal treatment;
(b) preparations intended for external use;
(c) Ophthalmic preparations and ear drops, and
(d) Sterile preparations such as sutures, surgical dressings and preparations intended for parenteral use.
(xii) Drugs and their preparations including combinations with other drugs imported into the country shall also bear on the label, the license number under which the drug is imported, preceded by the words "Import License" and the name and address of the importer.

(2) (i) The particulars to be printed or written on the label of a mechanical contraceptive shall be as specified in Schedule R.
(ii) The following particulars, in addition to those specified under sub-rule (1) shall be either printed or written in indelible ink and shall appear in a conspicuous manner on the label of the innermost container and on every other covering in which the container of a contraceptive, other than a mechanical contraceptive, is packed, namely-
(a) the date of manufacture;
(b) the date up to which the contraceptive is expected to retain its properties;
(c) the storage conditions necessary for preserving the properties of the contraceptive up to the date indicated in sub-clause (b):
Provided that for oral contraceptives it shall be sufficient to display on the lable of the container the date of manufacture only.

(3)(i) The particulars prescribed in sub-rule (1) shall be printed or written in indelible ink either on the label borne by a container or vaccine lymph or on a label or wrapper affixed to any package in which the container is issued for sale. The said particulars shall be indelibly marked on the sealed container of surgical ligature or suture or printed or written in indelible ink on the label enclosed therein.
(ii) Nothing in these rules shall be deemed to require the labelling of any transparent cover or of any wrapper, case or other covering used solely for the purpose of packing, transport or delivery.

(4) Where by any provision of these rules any particulars are required to be displayed on a label on the container such particulars may, instead of being displayed on a label, be etched, painted or otherwise indelibly marked on the container:
Provided that, except where otherwise provided in these rules, the name of the drug or any distinctive letters intended to refer to the drug shall not be etched, painted or otherwise indelibly marked on any glass container other than ampoules.
Explanation - For the purpose of this rule, the date of expiry shall be in terms of month and year and it shall mean that the drug is recommended till the last day of the month. The date of expiry shall be preceded by the words 'Expiry date'.

Rule 97. Labelling of medicines.
(1) The container of a medicine for internal use shall

(a) if it contains a substance specified in Schedule G, be labelled with the words 'Caution: it is dangerous to take this preparation except under medical supervision' - conspicuously printed and surrounded by a line within which there shall be no other words;
(b) if it contains a substance specified in Schedule H be labelled with the symbol Rx and conspicuously displayed on the left top corner of the label and be also labelled with the following words:
'Schedule H drug - Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only';
(c) if it contains a substance specified in Schedule H and comes within the purview of the 19[Narcotic Drugs and Psychotropic Substances Act, 1985 (61 of 1985)] be labelled with the symbol NRx which shall be in red and conspicuously displayed on the left top corner of the label, and be also labelled with the following words:
'Schedule H drug - Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only';
(d) if it contains a substance specified in Schedule X, be labelled with the symbol XRx which shall be in red conspicuously displayed on the left top corner of the label, and be also labelled with the following words :-
'Schedule X drug - Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only'.

(2) The container of an embrocation, liniment, lotion, ointment, antiseptic cream, liquid antiseptic or other liquid medicine for external application shall be labelled with the words in capital 'For External use only'.

(3) The container of a medicine made up ready only for treatment of an animal shall be labelled conspicuously with the words 'Not for human use; for animal treatment only' and shall bear a symbol depicting the head of a domestic animal.

(3A) The container of a medicine for treatment of food producing animals shall be labeled with the withdrawal period of the drug for the species on which it is intended to be used: Provided that if the specific withdrawal period has not been validated, the withdrawal period shall not be less than seven days for eggs or milk, twenty eight days for meat from poultry and mammals including fat and offal, five hundred degree days for fish meat.
Explanation:- For the purpose of this Rule, the withdrawal period is the period of interval between the last administration of a veterinary medicine to animals under the normal conditions of use and the production of food stuff from such animals to ensure that food stuffs do not contain residues in quantities in excess of the maximum residue limits laid down.

(4) The container of a medicine prepared for treatment of human ailments shall if the medicine contains industrial methylated spirit, indicate this fact on the label and be labelled with the words:
"For External use only"

(5) Substances specified in Schedule X in bulk form shall bear a label wherein the symbol as specified in sub-rule (1) shall be given conspicuously in red letters.

Rule 102. Non-Sterile Surgical Ligature and Suture. - Every container of, and wrapper enclosing surgical ligature or suture other than a ligature or suture offered or intended to be offered for sale as sterile, shall bear a label on which are printed or written in a conspicuous manner in indelible red ink the words "Non sterile surgical ligature (suture) - not to be used for operations upon the human body unless efficiently sterilized."

Rule 103.
(1) (Omitted)
(2) The name and address of the manufacturer shall be printed on the label of the container of a patent or proprietary medicine.
(3) The true formula or list of the ingredients shall be printed or written in indelible ink on the outer label of every package containing patent or proprietary medicine.

Rule 104. Use of letter I.P. etc. The letters 'I.P.' and recognised abbreviations of pharmacopoeias and official compendia of drugs standards prescribed under these rules shall be entered on the label of the drug only for the purpose of indicating that the drug is in accordance with standards set out in the Indian Pharmacopoeia or in any such pharmacopoeia or official compendium of drug standards recognised under the Rules.

Rule 104-A. Prohibition against altering inscriptions on containers, labels or wrappers of drug. -No person shall alter, obliterate or deface any inscription or mark made or recorded by the manufacturer on the container, label or wrapper of any drug **for use either for commercial sale or clinical trials or for any purpose approved by the licensing authority**:

Provided that nothing in this rule shall apply to any alteration, any inscription or mark made on the container, label, or wrapper of any drug at the instance or direction or with the permission of the Licensing Authority.

Rule 122-DA. Application for permission to conduct clinical ~~trails~~ **trials** for New Drug / Investigational New Drugs.-

(1) No clinical trial for a new drug, whether for clinical investigation or any clinical experiment by any institution, shall be conducted except under, and in accordance with, the permission, in writing, of the Licensing Authority defined in clause (b) of Rule 21.
(2) An application for grant of permission to conduct.-
(a) human clinical trials (Phase-I) on a new drug shall be made to the Licensing Authority in Form 44 **or Form 44A** accompanied by a fee of fifty thousand rupees and such information and data as required under Schedule Y;
(b) exploratory clinical trials (Phase-II) on a new drug shall be made on the basis of data emerging from Phase-I trial, accompanied by a fee of twenty-five thousand rupees;
(c) confirmatory clinical trials (Phase –III) on a new drug shall be made on the basis of the data emerging from Phase-II and where necessary data emerging from Phase-I also, and shall be accompanied by a fee of twenty-five thousand rupees;

Provided that no separate fee shall be required to be paid along with application for import/ manufacture of a new drug based on successful completion of phases clinical trials by the applicant:
Provided further that no fee shall be required to be paid along with the application by Central Government or State Government Institutes involved in clinical research for conducting trials for academic or research purposes.
(3) The licensing Authority after being satisfied with the clinical trials, shall grant permission in Form 45 or Form 45-A **or Form 45AA** or Form 46 or Form 46-A, as the case may be, subject to the conditions stated therein:
Provided that the Licensing Authority shall, where the data provided on the clinical trials is inadequate, intimate the applicant in writing, within ~~**six**~~ **four** months, from the date of such intimation or such extended period, not exceeding a further period of ~~**six**~~ **four** months, as the Licensing Authority may, for reasons to be recorded in writing, permit, intimating the conditions which shall be satisfied before permission could be considered.
Explanation:- For the purpose of these rules Investigational New Drugs means a new chemical
entity or a product having therapeutic indication but which have never been earlier tested on human beings.

122-DAA. Definition of Clinical trial.

~~**– For the purpose of this Part, "Clinical trial" means a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical pharmacological (including pharmacodynaic and pharmacokinetic) and/or adverse effects with the objective of determining safety and/or efficacy of the new drug.**~~

For the purpose of this part, "Clinical trial" means-

(i) in respect of drugs, any systematic study of investigational new drug or bioavailability or bioequivalence study in human participants to generate data for discovering or verifying its clinical, pharmacological, including pharmacodynamic and pharmacokinetic, or adverse effects with the objective of determining safety, efficacy or tolerance of the drug;
(ii) in respect of cosmetics, the systematic study, including dermatological study of any new cosmetic on human participants to generate data for discovering or verifying its adverse effects with the objective of determining safety, efficacy or tolerance of the cosmetic;
(iii) in respect of medical devices, the systematic clinical investigation or study of an investigational medical device or a new medical device in, or on human participants to assess the safety or performance or effectiveness of the medical device.

Rule 122 DAC. (1) Permission to conduct clinical trial:- The Licensing Authority as defined in clause (b) of Rule 21, on being satisfied that the data submitted along with the application in support of the proposed clinical trial is adequate in all respects, issue permission for conduct of clinical trial, subject to the following conditions, namely:-

(a) Clinical trial shall be conducted in compliance with the approved protocols, requirements of Schedule Y annexed to these rules, Good Clinical Practice Guidelines for conduct of clinical trials in India and other applicable regulations;
(b) Approval of the Ethics Committee shall be obtained before initiation of the study; (c) Clinical trial shall be registered at Clinical Trials Registry of India before enrolling the first patient for the study;
(d) Annual status report of each clinical trial, as to whether it is ongoing, completed or terminated, shall be submitted to the Licensing Authority and in case of termination of any clinical trial the detailed reasons for the same shall be communicated to the said Licensing Authority;
(e) Any report of serious adverse event occurring during clinical trial to the subject, after due analysis, shall be forwarded within ten days of its occurrence as per Appendix XI and in compliance with the procedures prescribed in Schedule Y;
(f) In case of an injury or death during the clinical trial to the subject of the clinical trial the applicant shall provide complete medical management and compensation in the case of trial related injury or death in accordance with Rule 122 DAB and the procedures prescribed under Schedule Y, and the details of compensation provided in such cases shall be intimated to the Licensing Authority within thirty days of the receipt of the order of the said authority;
(g) The premises of Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors and clinical trial sites shall be open to inspection by the officers authorized by the Central Drugs Standard Control Organization, who may be accompanied by an officer of the State Drug Control Authority concerned, to verify compliance to the requirements of Schedule Y, Good Clinical Practices guidelines for conduct of clinical trials in India and other applicable regulations;
(h) The Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors and clinical trial sites and the investigator shall allow officers authorized by the Central Drug Standard Control Organization, who may be accompanied by an officer of the State Drug Control Authority concerned, to enter with or without prior notice, any premises of sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors and clinical trial sites to inspect, search and seize any record, data, document, books, investigational drugs etc. related to clinical trials and provide adequate replies to any queries raised by the inspecting authority in relation to the conduct of clinical trial;
(2) Notwithstanding the conditions specified in sub-Rule (1), the Licensing Authority, on being satisfied that the data submitted along with the application in support of the proposed clinical trial is adequate in all respect, may also impose such additional conditions for issuance of permission in respect of specific clinical trials, if considered necessary, regarding the objective, design, subject population, subject eligibility, assessments, conduct and treatment of such clinical trial.
(3) If any Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors, Investigators conducting clinical trial and clinical trial sites fail to comply with any of the above conditions, the Licensing Authority, may, after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons thereof,-
(a) Issue warning letter giving details of deficiency found during the inspection, which might affect the right or well-being of the clinical trial subject or the validity of the study conducted at that site;

(b) Recommend that study may be rejected or discontinued; (c) Suspend or cancel the clinical trial permission;
(d) Debar the Investigator(s), Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors to conduct any clinical trial in future.
The Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors and clinical trial Investigators, against whom action as mentioned in sub-Rule (3) has been taken by the Licensing Authority, may, within ninety days of the receipt of the copy of the order of the Licensing Authority prefer an appeal to the Central Government, and the Central Government may, after giving such appellant an opportunity of being heard, confirm, reverse or modify such order.

Rule 122-DB . Suspension or cancellation of Permission/Approval.- If th e impor ter or manufacturer under this Part fails to comply with any of the conditions of the permissions or approval, the Licensing Authority may, after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefore, suspended or cancel it.

Rule 122-DC. Appeal.- Any person aggrieved by an order passed by the Licensing Authority under this Part, may within sixty days from the date of such order, appeal to the Central Government, and the Central Government may, after such enquiry into the matter as is considered necessary, pass such order in relation thereto as it thinks fit.

Rule 122 DD. Registration of Ethics Committee:-
(1) No Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with the Licensing Authority as defined in clause (b) of Rule
21: Provided that any Ethics Committee, existing on the date of commencement of the Drugs and Cosmetics (Third Amendment) Rules, 2013, who has already reviewed and accorded approval to clinical trial protocol, shall obtain registration within a period of forty-five days from the date of commencement of Drugs and Cosmetics (Third Amendment) Rules, 2013.
(2) An application for registration of Ethics Committee shall be made to the Licensing Authority in accordance with the requirements as specified in the Appendix VIII of Schedule Y.
(3) The Licensing Authority after being satisfied that the requirements have been complied with, may grant registration to the Ethics Committee subject to such conditions as may be stated therein.
(4) The Ethics Committee shall review and accord its approval to a clinical trial and also carry ongoing review of the trial at appropriate intervals, as specified in Schedule Y, and the Good Clinical Practice Guidelines for Clinical Trials in India and other applicable regulatory requirements for safeguarding the rights, safety and well-being of the trial subjects.
(5) In the case of any serious adverse event occurring to the clinical trial subjects during the clinical trial, the Ethics Committee shall analyze and forward its opinion as per procedure specified under APPENDIX XII of Schedule Y.
(6) The Ethics Committee shall allow inspectors or officials authorized by the Central Drugs Standard Control Organization to enter its premises to inspect any record, data or any document related to clinical trial and provide adequate replies to any query raised by such inspectors or officials, as the case may be in relation to the conduct of clinical trial.

(7) The registration, unless it is suspended or cancelled, shall be valid for a period of three years from the date of issue:
Provided that if the application for ~~**reregistrtion**~~ **re-registration** is received by the Licensing Authority within three months before the expiry, the registration shall continue to be in force until orders are passed by the said authority:
Provided further that the Licensing Authority shall be informed in writing in case of any change in the membership or the constitution of the Ethics Committee takes place.
(8) If the Licensing Authority is not satisfied, he shall reject the application and shall inform the applicant of the reasons for such rejection and the conditions which must be satisfied before the registration can be granted.
(9) If the Ethics Committee fails to comply with any of the conditions of registration, the Licensing Authority may, after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefor, suspend or cancel the registration of the Ethics Committee for such period as considered necessary.
(10) The Ethics Committee whose registration has been suspended or cancelled by the Licensing Authority, may, within ninety days of the receipt of the copy of the order, prefer an appeal to the Central Government and the Central Government may after giving an opportunity of being heard, confirm, reverse or modify such order.
Explanation:- For the purpose of this Rule an Ethics Committee is a committee comprising of medical, scientific, non-medical and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and will-being of human subjects involved in a clinical trial and it shall be responsible for reviewing and approving the protocol, the suitability of the investigators, facilities, methods and adequacy of information to be used for obtaining and documenting informed consent of the study subjects and adequacy of confidentiality safeguards.